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Adult human hippocampal neurogenesis – controversy and evidence

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Abstract: The hippocampus has been described as one of the few sites in the mammalian brain capable of generating new cells continuously throughout life. Two recent studies that report contradicting findings on adult human hippocampal neurogenesis, however, reminds us of the caveats and challenges of studying this phenomenon in post-mortem tissues.

Keywords: adult neurogenesis, hippocampus

It has been 56 years since the first evidence of adult hippocampal neurogenesis in the mammalian system was reported [1] and 20 years since it was first demonstrated in the human brain [2]. Despite substantial supporting data existing, recent contradicting reports by Sorrells and colleagues [3] and Boldrini and colleagues [4] showed that the very existence of human hippocampal neurogenesis can still be a subject for debate.

Sorrells and colleagues [3] examined 18 adult and 19 perinatal or postnatal post-mortem brain tissues obtained from individuals of wide age range (14 gestational weeks to 77 years) with various causes of death (full medical history was not provided by the authors). Upon extensive immunohistochemical analysis of cells labelled with markers for proliferation (Ki-67$^+$), young immature neurons (DCX/PSA-NCAM$^+$), radial glia-like stem cells, and glia in the

hippocampus, they observed the highest number of proliferating cells and young immature neurons during the first year of life in the dentate gyrus (DG), which has been known to be the primary site of adult hippocampal neurogenesis. In line with the existing literature [5, 6], they reported a sharp age-dependent decrease in the number of these cells. Only a few isolated young neurons were observed by 7 and 13 years of age. No young neurons were detected in the DG of adult patients with epilepsy or healthy adults. A similar age-dependent reduction was also seen in rhesus macaques.

On the other hand, Boldrini and colleagues [4] examined 28 post-mortem hippocampal tissues derived from healthy adults "without cognitive impairment, neuropsychiatric disease, or (history of medical) treatment" in the range of 14 to 79 years of age. They used similar immunohistochemistry methods as Sorrells and colleagues did to visualize various cell types relevant to hippocampal neurogenesis, including the quiescent neural progenitors, proliferating intermediate progenitors, young immature neurons, and mature granule neurons. They subdivided the DG to anterior, mid, and posterior based on the relative location of the DG to the lateral geniculate visible on the coronal planes of the brain sections.

In contrast to Sorrells and colleagues' observations, Boldrini and colleagues were able to detect all of the immature and mature cell types in the adult human DG as shown in previous other studies [2, 7, 8]. Furthermore, they did not observe a substantial decline in the number of these cells with age. The number of cells for each cell type were estimated to be at least thousands per DG sub-region, supporting a previous study that showed similar numbers for adult-born hippocampal cells [6]. Most of these cell types were stably detected

across age, except for quiescent neural stem cells (GFAP/Sox2/Nestin^{+}) which showed an age-dependent decrease specifically in the anterior-mid DG. They also found that the DG volume remained largely unchanged, whereas measures for neuroplasticity and angiogenesis declined with age in the anterior DG. This concomitant decrease was also found to be significantly correlated with each other.

At first, it may seem surprising that the two studies used similar methods and reached completely opposite conclusions as to whether adult human hippocampal neurogenesis exists. However, a closer look at the subtle differences in their methods may provide clues to why this might have happened.

One of the key strengths of Boldrini and colleagues' study, not implemented by Sorrells and colleagues, is the use of stereology—widely regarded as the gold standard for unbiased quantification in histological studies. The adult brains examined by Sorrells and colleagues also had at least 20 hours longer post-mortem delay compared with those used by Boldrini and colleagues, which may have further diminished the immunoreactivity of markers such as DCX [9]. Furthermore, the majority of control adults studied by Sorrells and colleagues were diagnosed with various diseases such as cancer and stroke, whereas Boldrini and colleagues have taken rigorous measures to ensure that their subjects were physically and psychologically healthy. Therefore, it is difficult to say that the findings of Sorrells and colleagues represent adult human hippocampal neurogenesis in the general population, and there is a high chance that Boldrini and colleagues were more likely to have generated accurate estimates of neurogenesis in healthy human adults using a bias-free approach, such as stereology.

However, despite the fact that Boldrini and colleagues used more reliable methods to study neurogenesis compared with Sorrells and colleagues, both studies share common grounds in a way that they clearly demonstrate the limitations of studying this phenomenon in human post-mortem brain tissues.

The markers that both research groups used are largely derived from characterisation studies based on rodent models, and indeed, the majority of them have been shown to label post-mortem human tissues in a similar pattern. However, species differences could make it difficult to generate "reproducible" results when applying the same markers to study humans, and thus, raises the necessity of developing a different set of markers that can be readily used to detect the cell-type of interest more reliably in humans. Notably, the absence of a proxy for *in vivo* human hippocampal neurogenesis may be the biggest obstacle hindering our progress in understanding the functional aspects of adult-born neurons in the hippocampus.

To actively address this issue, one could start by investigating the gene expression changes in the developing human brain at the transcriptomic level. Single-cell RNA-sequencing analysis on post-mortem brain tissues that spans a wide range of age, for example, would help us to choose better molecular markers of human hippocampal neurogenesis. Advancements in non-invasive imaging and bio-marker studies would also help us to investigate the role of adult-born neurons at the neural circuitry level and study the functional relevance of these neurons directly in human participants in the context of many

interesting subjects that neurogenesis has been previously associated with, such as cognition, mental health, and lifestyle [10].

As demonstrated by both groups of researchers, adult human hippocampal neurogenesis can still be a hotly debated subject and calls for a direct, reliable, and reproducible proxy or marker of *in vivo* human hippocampal neurogenesis. As two sides of the same coin, the two studies provide a push to the field to develop more advanced tools and models that will generate functionally relevant data for human hippocampal neurogenesis.

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